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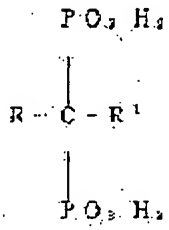
(54) OSTEOGENESIS STIMULATING AGENT

(57)Abstract:
PURPOSE: To obtain a new osteogenesis stimulating agent having osteogenesis stimulating activity based on calcification stimulating activity, etc., of an osteoblast by compounding specific bisphosphonic acid or its salt as an active component.
CONSTITUTION: This is an osteogenesis stimulating agent containing a bisphosphonic acid of the formula [R is H2N(CH2)n [(n) is an integer of 2-5] or CH3; R1 is OH] or its salt as an active component. As the bisphosphonic acid or its salt, especially 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate is preferable. The osteogenesis of the agent is based on calcification stimulating activity or bone matrix production-stimulating activity of an osteoblast, or is dependent on 1α, 25-dihydroxyvitamin D3. The osteogenesis stimulating agent is preferably formulated as an oral tablet or an injection.



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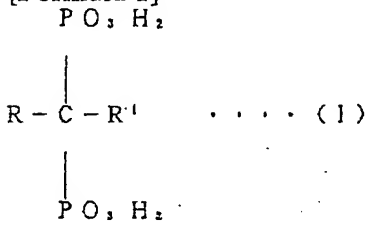
CLAIMS

[Claim(s)]
[Claim 1] The following formula (I)
[Formula 1]



R expresses H2 N-(CH2) n- (n expresses the integer of 2-5), or CH3- among [formula, and R1 expresses -OH.] The osteogenesis accelerator which comes out and makes an active principle the screw ******** acid shown or its salt.
[Claim 2] The osteogenesis accelerator according to claim 1 whose osteogenesis promotion is a thing based on a mineralization promotion operation of an osteoblast.
[Claim 3] The osteogenesis accelerator according to claim 1 or 2 whose osteogenesis promotion is a thing based on a bone-matrix production promotion operation of an osteoblast.
[Claim 4] Osteogenesis promotion is 1alpha and 25-dihydroxy vitamin D 3. Osteogenesis accelerator of the claim 1-3 which is the thing of a dependency given in any one term.
[Claim 5] The osteogenesis accelerator of the claim 1-4 whose R is H2 N-(CH2)3- given in any one term.
[Claim 6] The osteogenesis accelerator of the claim 1-4 whose R is CH3- given in any one term.
[Claim 7] The osteogenesis accelerator of the claim 1-4 a screw ******** acid or its salt of whose is 4-amino-1-hydroxy butylidene -1, and a 1-screw ******** acid monochrome Na salt and a ****** id rate given in any one term.
[Claim 8] the type where it was suitable for internal use -- **** -- the osteogenesis accelerator of the claim 1-7 it comes-izing [claim] given in any one term
[Claim 9] The osteogenesis accelerator of the claim 1-7 whose tablet is the injection given in any one term.

[Translation done.]

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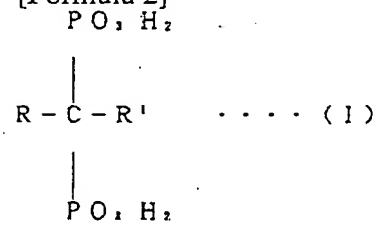
DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] this invention relates to an osteogenesis accelerator. this invention relates to the osteogenesis accelerator which makes an active principle a screw ******** acid or its salt still in detail.
[0002]
[Description of the Prior Art] A screw ******** acid is the derivative of the pyrophosphoric acid which exists in the living body. It has powerful bone-resorption depressant action. [Fleisch H., Bisphosphonates-history and experimental basis, Bone 1987, and 8(suppl.1); S23-S28], ********** (Paget's) disease () [Kanis] JA.Drags used for the treatment of Paget's disease of bone, London, Martin Dunitz Ltd., and 1991, 159 and 216, The hypercalcemia accompanied by bone transition and the malignant tumor of cancer () [Fleisch H. and] [Bisphosphonates:pharmacology and use in the treatment of tumour-induced] hypercalcaemic andmetastatic bone disease, Drugs 1991, 42,919-944, and osteoporosis () [Watts NB, Harris ST, Genant HK, et al.,] [Intermittent cyclical] etidronatetreatment of postmenopausal osteoporosis and N.Engl.J.Med. -- it has been effectively used to a control of the osteolysis in 1990, 323, 73-79, etc., or suppression of a bone quantity decrement
[0003] That it is a bone-resorption inhibitor also with powerful 4-amino-1-hydroxy butylidene -1 and 1-screw ******** acid (allene **********) which are one of such screw ******** acids in vitro () [Sato M,] [Grasser] J.BoneMiner. W. -- Effects of bisphosphonates-isolated rat osteoclasts as examined by reflected light microscopy -- Res., 1990 and 5, 31-40, Laboratory animal () [Thompson DD,] [Seeder] JG, Quartuccio H, et al., and The bisphosphonate, alendronate, prevents bone loss in ovariectomized baboons, J.Bone Miner.Res., 1992, 7,951-960, etc., Paget's disease () [O'Doherty DP,] [Gertz] BJ, Tindale W, et al., and Effects of five daily -- 1h infusions of alendronate in Paget's desease of bone and J.Bone Miner.Res. -- JP,2-13645,B, such as 1992, 7, and 81-87, -- JP,4-211015,A, And an osteoporosis patient () [Harris ST,] [Gertz] BJ, Genant HK, et al., and The effect of short term treatment with alendronate ON vertebral density and biochemical markers It is checked in ofbone remodeling in early postmenopausal women, J.Clin.Endocrinol.Metab., 1993 and 76, and 1399-1406.
[0004] Since the screw ******** acid had the important operation to the bone resorption, many of the researches focused on this bone-resorption depressant action until now (Sato M., Grasser W., Endo N., et al, Bisphosphonate action:Alendronate localization inrat bone and effects-osteoclast ultrastructure, J.Clin.Invest 1991, and 88:2095-2105).
[0005] on the other hand, as a report of the direct operation to the osteogenesis of a screw ******** acid In an osteoblast Osteogenesis depressant action accepted (). [Lemkes] HHPJ, Reitsma PH, and Frijlink W. -- et al. and A new diphosphonate -- Dissociation beteen effects oncells and mineral in rats and a preliminary trial in Paget's disease, Adv.Exp.Med.Biol., 1978 and 103, 459-469, In an osteoblast The elevation operation of the function accepted (). [Felix] R and Fleisch H.Increase Although there are in alkaline phosphatase activity in calvaria cells cultured with diphosphonates, Biochem.J., 1979 and 183, 73-81, etc. No publication is made about the osteogenesis promotion operation.
[0006] On the other hand Tenenbaum HC and Torontali M. -- Sukhu B. -- Effects of bisphosphonates and inorganic pyrophosphate ON osteogenesis in vitro, Bone, 1992, 13,249-255 and Hankel LS, McBride DJ, Shapiro JR., and Bisphosphonates enhance mineralization in a chick osteoblast cell culture system

(abstract), Bone Miner.Res., and 1992 and 7 (suppl.1)s722 Each has tried [in / the osteoblast of a fowl / then] the study of the operation to the osteogenesis of a screw ******** acid.
[0007] however, Tenenbaum ** -- **** -- the opposite result called a promotion operation and depressant action of a mineralization by high-concentration (more than 3x10-8M) ********** and ********** is obtained -- it is not alike too much Moreover, in Hankel et al., although the mineralization promotion operation accepted by high-concentration ********** etc., in order not to accept change in a collagen but to say it clinically from these results that an osteogenesis promotion operation is accepted in a screw ******** acid, it cannot necessarily be said that it is enough.
[0008]
[Problem(s) to be Solved by the Invention] Then, the purpose of this invention is to offer a new osteogenesis accelerator.
[0009]
[Means for Solving the Problem] Using a Homo-sapiens osteoblast Mr. cell, this invention considers the influence to in vitro mineralization and bone-matrix protein synthesis about a screw ******** acid, especially allene **********, and, as a result, reaches.
[0010] That is, this invention is the following formula (I).
[0011]
[Formula 2]



(I)

R expresses H2 N-(CH2) n- (n expresses the integer of 2-5), or CH3- among [formula, and R1 expresses -OH.] It is the osteogenesis accelerator which comes out and makes an active principle the screw ******** acid shown or its salt.
[0012] The osteogenesis accelerator of this invention means the thing based on a mineralization promotion operation of an osteoblast, and/or a bone-matrix production promotion operation, and it is based on promoting as latter synthesis of an osteocalcin, a collagen, etc. which are bone-matrix protein, for example by promoting the calcium to an osteoid layer, and the deposition of Lynn as former, for example. Especially, the osteogenesis accelerator based on a mineralization promotion operation of an osteoblast and a bone-matrix production promotion operation can be mentioned as a desirable thing.
[0013] Furthermore, 1alpha and 25-dihydroxy vitamin D 3 By the meaning of acting cooperatively an operation of the factor (it abbreviating to an osteogenesis promoter hereafter) which promotes a mineralization of an osteoblast [like] with promotion and/or this, osteogenesis promotion of the osteogenesis accelerator of this invention is 1alpha and 25-dihydroxy vitamin D 3. What is a thing of a dependency is contained in the domain of this invention. That is, they are this 1alpha and 25-dihydroxy vitamin D 3 as a thing desirable as an osteogenesis accelerator of this invention. The thing based on the operation combined with the mineralization promotion operation of a dependency and the above-mentioned osteoblast and/or the bone-matrix production promotion operation can also be mentioned.
[0014] As a screw ******** acid shown by the aforementioned formula (I) For example, 6-amino-1-hydronalium ****** xylidene -1, 1-screw ******** acid, 5-amino-1-hydroxy pen dust DIN -1, 1-screw ******** acid, 4-amino-1-hydroxy butylidene -1, 1-screw ******** acid (allene **********:alendronate), The 3-amino-1-hydroxy propylidene -1, 1-screw ******** acid (**********:pamidronate), and ********** (etidronate) Although mentioned Also in these, allene **********, **********, and ********** are desirable and can mention allene ********** as a desirable thing especially.
[0015] As a salt of the screw ******** acid of this invention, organic acid chloride, such as inorganic-acid

salts, such as alkaline-earth-metal salts, such as alkali-metal salts, such as the salt permitted pharmacologically, for example, sodium, and a potassium, and calcium, and a hydrochloride, a citric acid, and an amino acid salt, etc. is mentioned, and the monosodium salt and ****** id rate of allene ********** can be mentioned as a desirable thing from the point of excelling water-soluble especially.
[0016] Each screw ******** acid shown by the aforementioned formula (I) of this invention is a well-known compound. By for example, the technique indicated by JP,2-13645,B, JP,61-109794,A, JP,3-101684,A, JP,5-132492,A, JP,4-211015,A, etc. Allene **********, or its monosodium salt and ****** id rate, Salts, such as potassium salt and a calcium salt, can be obtained. by for example, the technique indicated by the West German patent specification of No. 2130794, the U.S. patent specification of No. 4327039, etc. ********** or its salt can be obtained by the technique indicated by U.S. JP,3468935,B, No. 3400147, or the No. 3475486 specification in ********** or its salt.
[0017] The screw ******** acid or its salt of this invention can be prescribed for the patient taking-orally-wise with either of the suitable pharmacology scholarly simple substances for [, such as the injection,] parenteral medication. the dose -- the person's prescribed a medicine for the patient age, the eucrasia, and weight -- it will be dependent on the modality of combined use treatment, the frequency of the treatment, and the modality of effect desired supposing it is carrying out
[0018] Generally, in osteoblast level, the amount of whole body-Japanese of an active-ingredient compound is 10-13-10-7M, and is [kg] 0.01micro [per weight kg] g-0.1mg preferably about 0.001 microg/kg - 1mg /. Usually, in the case of internal use, in the case of a parenteral administration, it will be a 0.5ng/day -0.5mg/day a 50ng/day -50mg/day. Moreover, the need is embraced, for example, they are 1alpha and 25-dihydroxy vitamin D 3. [1alpha, 25(OH) 2 D3]1alpha-hydroxy vitamin D 3 It can also use together with hormone drugs, such as active-vitamin-D 3 kind of a grade, and estrogen.
[0019] In the case of internal use, the osteogenesis accelerator of this invention is a tablet, a capsule, a powder parcel, a liquid solution, suspension, or the prescribed [for the patient] type like an elixir of a medicine, and, in parenteral use, can be used as a solution or non-fungus liquid for prescription like suspension.
[0020] As an excipient in such a case, it is suitably tablet-ized combining a fatty alcohol, talc, aromatic ester, water, physiological salines, and alcohols, for example, ethyl alcohol, such as rubber, such as sugar, for example, a saccharose, a glucose, a lactose, starch, a cellulose and its derivative, for example, carboxymethylcellulose sodium, and an ethyl cellulose, a fatty acid and its salt, a polyol, for example, a propylene glycol, a glycerol, a sorbitol, a mannitol, and a polyethylene glycol, a triglyceride, fatty acid ester, etc.
[0021] unless the osteogenesis accelerator of this invention is independent or it is contrary to the purpose of this invention -- other medicines -- mixing -- or -- each -- **** -- tablet-izing -- a medicine can be prescribed for the patient The osteogenesis promoter described above as such other medicines, for example, 1alpha, and 25-dihydroxy vitamin D 3 Cytokines, such as vitamin K, IL-4, IGF-I, or TGF-beta, can be mentioned, and the domain of the amount of prescription in the case of usually prescribing these factors for the patient as a medicine as dose of these factors in such a case can be mentioned.
[0022] Although the osteogenesis accelerator of this invention is obtained in this way, since the osteogenesis accelerator of this invention has a mineralization promotion operation and a bone-matrix production promotion operation as mentioned above, it is useful to a prevention of an osteomalacia, an osteogenesis imperfecta, osteoporosis, the bone dystrophy based on secondary nature hyperparathyroidism, a ****** dystrophy, and gum disease, the treatment and treatment promotion of fracture, and orthodontics, for example.
[0023]
[Example] Hereafter, an example is given and this invention is explained still in detail.
[0024] In addition, an osteoblast Mr. cell, a measuring method, etc. which were used are as follows.
(1) As a cell culture Homo-sapiens periosteum origin osteoblast Mr. cell, the cell of a 10 years-old boy's femur origin was used (the Tokyo old-man research institute and Dr. **** Yasuko). namely, alpha-glycerophosphoric-acid-2Na(alpha-GP) [Tokyo -- formation -- by incubation with] made from Industry and 1alpha, and 25(OH)2 D3, high alkaline-phosphatase (alkaline phosphatase:ALP) activity is

shown, and osteocalcin (BGP) production and a mineralization start
[0025] About manufacture of a cell, and a cultivation, it is Biochem.Biophys.Res.Commun., 1987 and 145, 651-657, In Vitro Cell.Biol., 1989 and 25, 37-43, Connect.Tiss., 1993, and 24.217-231 (all are the work of Koshihara Y and et al.). It carried out by following. concrete -- cell-population twice -- number (population doubling level, PDL) of-izing 19 (Hereafter) The cell of 19PDL 6 or 12-well culture plate It cultivates in [which uses and contains a fetal calf serum (FBS) (product made from Irvine scientific) 10%] alpha-minimum essential medium (made in LIFE (alpha-MEM) Technologies). Eagle's (37 degrees C) 5%CO2/95%air It carried out. They are 1alpha and 25(OH)2 D3 two - three days after confluent attainment (20PDL) and under the alpha-GP presence of 2mM. Predetermined term incubation was further carried out by addition or un-adding. 1alpha and 25(OH)2 D3 It saved at -20 degrees C as an ethanol solution, and it added in the incubation system so that the last concentration of ethanol might become 0.1% (v/v). The screw ******** acid was saved at 4 degrees C as a phosphate-buffered saline solution (PBS), respectively, and it was added in the incubation system so that the last concentration of PBS might become 0.1% (v/v). Culture medium was exchanged 3 times per week.
[0026] (2) total RNA was prepared by the AGPC method (Anal.Biochem., 1987 and 162, 156-159) from the RT-PCR (reverse transcription-polymerase chain reaction) Homo-sapiens osteoblast Mr. cell. total RNA1microg to cDNA was compounded (37 degrees C, 60 minutes). Pro As a specific primer to an alpha1(I) collagen gene and BGP gene It is HCOLA-1A (), respectively. [5'-CCA] CCG ACC AAG AAA CCA-3' And HCOLA-1B () [5'-GCT CAC] CAG GAC GAC CAG-3' HBGP-1A (5'-CCT CAC ACT CCTCGC CCT ATT-3') and HBGP-1B (5'-ATA GGC CTC CTG AAA GCC GAT-3') are used. thermocycler oven (product made from a MiniCycler PTC-150;MJ research) PCR amplification was performed in inside. It is the denaturation (denaturation) for 2 minutes to the beginning. annealing for 94 degrees C after carrying out, the denaturation for 1 minute, 55 degrees C (BGP) or 60 degrees C [pro alpha1(I) collagen], and 2 minutes, 72 degrees C, and extension for 3 minutes 30 cycle ******. After electrophoresis and PCR production were dyed by ethidium bromide on the agarose gel, and a photograph was taken in the photograph (Polaroid ACMEL M-085 Auto).
[0027] (3) Calcium (calcium) Lynn (Pi) ALP activity and the determination ALP activity of BGP, collagen, and DNA measured p-nitroglycerine phenyl phosphate [the product made from Sigma Chemistry] as a substrate by the technique of Maio and de Carli (Nature 1962, 196, and 600-601). That is, a cell is washed 3 times with a physiological salt solution after an incubation end, and it is 10mMp. - The nitroglycerine phenyl phosphate-1mMMgCl2-0.1M carbonate buffer (pH10.0) was added, and was made to react for 15 - 20 minutes. The reaction mixture was moved and the absorbance in 415nm was measured.
[0028] After washing the cell after ALP activity-measurement reaction with a physiological salt solution again, operation of having added perchloric acid (PCA) 5% and extracting calcium and Pi (inside of iced water for 15 minutes) was repeated twice, and was performed. The content of calcium and Pi is the o-cresolphthalein compexone (OCPC) method (Anal.Biochem.1967, 18, and 521-531), respectively. And determination was carried out by Chen's et al. technique (Anal.Chem., 1956, 28, 1756-1758).
[0029] BCP carried out the ultrasonic spallation of the cell in 20% formic acid, extracted, and after it freeze-dried, it was saved at -80 degrees C to measurement. Measurement is Gla-Osteocalcin. It was based on the enzyme immunoassay using the measurement kit [the TAKARA SHUZO CO., LTD. make].
[0030] Kivirikko after hydrolyzing the amount of collagens of the stratum compactum with 6N hydrochloric acid (the inside of an autoclave, for 130 degrees C and 30 minutes) ** -- technique (Anal.Biochem., 1967, 19,249-255) It followed, and determination of the hydroxyproline was measured and carried out.
[0031] After carrying out PCA extraction of the DNA content, it was measured by the Burton method (Biochem.J., 1956, 62,315-323).
[0032] (Example 1) Into the Homo-sapiens osteoblast Mr. cell of 20PDL which reached the influence confluence exerted on a mineralization of the Homo-sapiens osteoblast Mr. cell of a screw ******** acid, allene ********** or ********** of the concentration (10-12 M-10-5M) shown in drawing 1 was added, and it cultivated for seven days into it, under 1alpha, 25(OH)2 D3, and (100 ng/ml) 2mMalpha-GP presence.

[0033] As an example of a contrast, they are 1alpha and 25(OH)2 D3. According to the aforementioned calcium assay, determination of the calcium content of the Homo-sapiens osteoblast Mr. stratum compactum after incubation was carried out for seven days using the independent thing. The result was shown in drawing 1 . In drawing 1 , each column shows an average ** standard error (three examples). The statistical significant difference with a contrast is * :P <0.05, ** :P <0.01, *** :P It is <0.001.
[0034] drawing 1 to allene ********** -- 10-12 -- the concentration which is -10-7M -- 100 ng/ml 1alpha and 25(OH)2 D3 calcium deposition (mineralization) of the Homo-sapiens osteoblast Mr. cell cultivated for seven days under presence is promoted, and it turns out that this is suppressed conversely by the concentration beyond 10-6M. A mineralization promotion operation is 1alpha and 25(OH)2 D3, although it became the maximum in the 10-9M neighborhood. Such a facilitatory effect did not accept under un-existing (data ******).
[0035] Similarly, ********** also promoted the mineralization of a Homo-sapiens osteoblast Mr. cell in low concentration (10-10 -10-8M), and suppressed this more than by 10-6M. Although the minimum useful density of ********** in a mineralization promotion operation was high at least 100 times compared with it of allene **********, the manifestation concentration of the mineralization depressant action by the side of high concentration did not almost have a difference from both the screws ******** acid. In addition, although not shown in data, change of Pi content by allene ********** and ********** was the same as that of a mineralization promotion operation.
[0036] (Example 2) Into the Homo-sapiens osteoblast Mr. cell of 20PDL which reached the influence confluence exerted on a mineralization of the Homo-sapiens osteoblast Mr. cell of allene **********, allene ********** of the concentration (10-14 M-10-9M) shown in drawing 2 was added, and it cultivated for 14 days into it, under 1alpha, 25(OH)2 D3, and (100 ng/ml) 2mMalpha-GP presence. As an example of a contrast, they are 1alpha and 25(OH)2 D3. Using an independent thing, determination of the calcium content of the Homo-sapiens osteoblast Mr. stratum compactum after incubation will be carried out for 14 days like an example 1, and a result is shown in drawing 2 . In drawing 2 , each column shows an average ** standard error (six examples). The statistical significant difference with a contrast is * :P <0.05, *** :P It is <0.001.
[0037] Drawings 2 -1alpha and 25(OH)2 Under the condition which adds D3 (100 ng/ml), and will cultivate a cell for 14 days, although the mineralization promotion operation by allene ********** hardly accepts in 10-14M, it turns out that it is discovered clearly from 10-13 M.
[0038] (Example 3) Allene ********** was added into the Homo-sapiens osteoblast Mr. cell of 20PDL which reached the influence confluence exerted on BGP production and collagen production of allene ********** of a Homo-sapiens osteoblast Mr. cell, and it cultivated for ten days into it, under 2mMalpha-GP presence and 1alpha, 25(OH) 2 D3 presence (10 ng/ml), or un-existing. Using allene ********** a non-adding thing as an example of a contrast, according to the aforementioned technique, determination of BGP and the amount of collagens of the stratum compactum is carried out, and a result is shown in the drawing 3 and the drawing 4 . In drawings 3 and 4, each column shows an average ** standard error (four examples). The statistical significant difference with a contrast is * :P <0.05, ** :P It is <0.01. The concentration (10-11 M) below the minimum useful density (10-13 M) in a mineralization promotion operation and the maximum effect manifestation concentration was used for allene **********.

[0039] drawing 3 to allene ********** -- 1alpha and 25(OH)2 -- D3 It turns out that BGP production is notably promoted under presence. Moreover, drawing 4 to allene ********** is 1alpha and 25(OH)2 D3 about collagen production. It turns out that it promotes intentionally under presence.
[0040] (Example 4) BGP and pro of the Homo-sapiens osteoblast Mr. cell of allene ********** Allene ********** of the same concentration as having used for the Homo-sapiens osteoblast Mr. cell of 20PDL which reached the influence confluence exerted on the gene expression of alpha 1(I) collagen in the example 3 was added, and it cultivated for 3, 7, or 14 days under 2mMalpha-GP and 1alpha, and 25(OH) 2 D3 presence (10 ng/ml). As an example of a contrast, they are 1alpha and 25(OH)2 D3. According to the aforementioned technique, total RNA of a cell is extracted using an independent thing, and they are BGP and pro. The gene expression of alpha 1(I) collagen was examined. A result is shown in the drawing 5 (a)

(BGP gene expression) and a (b) [pro alpha1(I) collagen gene expression.
[0041] which [from drawing 5 (a)] time -- also setting -- allene ********** -- 1alpha and 25(OH)2 -- D3 Although it has not checked promoting further BGP gene expression guided powerfully 1alpha and 25(OH)2 D3 Since BGP gene expression is already guided powerfully independently, by this system of measurement, it is thought that the manifestation beyond it by allene ********** was fully undetectable. On the other hand, allene ********** from drawing 5 (b) is 1alpha and 25(OH)2 D3. Guided pro It turns out that the gene expression of alpha 1(I) collagen is further promoted in concentration dependence at all the times.
[0042] It is as above low concentration more nearly further than the manifestation concentration of the bone-resorption depressant action well known as an operation of a screw ******** acid until now, and allene ********** and ********** are 1alpha and 25(OH)2 D3. The mineralization of a Homo-sapiens osteoblast Mr. cell was promoted under presence. Production and pro of BGP and collagen which are bone-matrix protein at the mineralization promotion by allene ********** Since it was accompanied by promotion of mRNA manifestation of alpha 1(I) collagen, it was thought that it was not what is depended on the physical chemistry-property of a screw ******** acid.

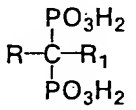
[Translation done.]

JP7-330613 (Teijin); Bone formation accelerating agents

[Claim 1]

Bone formation accelerating agents containing bis-phosphonic acid(s) or its salt form(s) as active ingredient(s) possessing the structure depicted in Structure 1.

Structure 1.



R is H_2N-$(CH_2)_n$- (n=2-5), or CH_3-
R_1 is -OH

Comments: Structure 1 is aleudronate when n=3.

[Claim 2]

Bone formation accelerating agents described in claim 1, where bone formation acceleration takes place as a result of increased calcification caused by the action of osteoblast cells.

[Claim 3]

Bone formation accelerating agents described in claim 1 or 2, where bone formation acceleration takes place as a result of increased bone matrix formation caused by the action of osteoblast cells.

[Claim 4]

Bone formation accelerating agents described in claim 1, 2, or 3, where bone formation acceleration is dependent upon 1a,25-dihydroxy vitamin D_3.

[Claim7]

Bone formation accelerating agents described in claim 1, 2, 3 or 4, where the bis-phosphonic acid or its salt is 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid mono Na-salt trihydrate.

Comments: isn't this aleudronate itself?

Translated from Japanese
April 11, 2001
Hiroo Koyama (x43004)